

(FILE 'HOME' ENTERED AT 14:41:34 ON 26 FEB 2002)

FILE 'MEDLINE, AGRICOLA, CANCERLIT, SCISEARCH, CAPLUS, BIOSIS, MEDICONF'
ENTERED AT 14:52:52 ON 26 FEB 2002

L1 21 S DAF-18 AND PTEN
L2 3582 S DAF-18 OR DAF18 OR PTEN
L3 21 S L1 AND (ELEGANS OR MAMMAL)
L4 5 DUP REM L3 (16 DUPLICATES REMOVED)
L5 5 SORT L4 PY
L6 200 S L2 AND PY<=1997
L7 100 DUP REM L6 (100 DUPLICATES REMOVED)
L8 53 S L7 AND (MODULATE? OR INCREASE? OR DECREASE? OR ENHANCE? OR S
L9 53 SORT L8 PY
L10 3 S L9 NOT PTEN

=> d an ti so au ab pi l5 1-5

L5 ANSWER 1 OF 5 MEDLINE
AN 1999102962 MEDLINE
TI The C. **elegans** **PTEN** homolog, **DAF-18**
, acts in the insulin receptor-like metabolic signaling pathway.
SO MOLECULAR CELL, (1998 Dec) 2 (6) 887-93.
Journal code: C5E; 9802571. ISSN: 1097-2765.
AU Ogg S; Ruvkun G
AB An insulin-like signaling pathway, from the DAF-2 receptor, the AGE-1 phosphoinositide 3-kinase, and the AKT-1/AKT-2 serine/threonine kinases to the DAF-16 Fork head transcription factor, regulates the metabolism, development, and life span of *Caenorhabditis elegans*. Inhibition of **daf-18** gene activity bypasses the normal requirement for AGE-1 and partially bypasses the need for DAF-2 signaling. The suppression of age-1 mutations by a **daf-18** mutation depends on AKT-1/AKT-2 signaling, showing that **DAF-18** acts between AGE-1 and the AKT input to DAF-16 transcriptional regulation. **daf-18** encodes a homolog of the human tumor suppressor **PTEN** (MMAC1/TEP1), which has 3-phosphatase activity toward phosphatidylinositol 3,4,5-trisphosphate (PIP3). **DAF-18** **PTEN** may normally limit AKT-1 and AKT-2 activation by decreasing PIP3 levels. The action of **daf-18** in this metabolic control pathway suggests that mammalian **PTEN** may modulate insulin signaling and may be variant in diabetic pedigrees.

L5 ANSWER 2 OF 5 MEDLINE
AN 1999307426 MEDLINE
TI The **PTEN** tumor suppressor homolog in *Caenorhabditis elegans* regulates longevity and dauer formation in an insulin receptor-like signaling pathway.
SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1999 Jun 22) 96 (13) 7427-32.
Journal code: PV3; 7505876. ISSN: 0027-8424.
AU Mihaylova V T; Borland C Z; Manjarrez L; Stern M J; Sun H
AB Inactivation of the tumor suppressor **PTEN** gene is found in a variety of human cancers and in cancer predisposition syndromes. Recently, **PTEN** protein has been shown to possess phosphatase activity on phosphatidylinositol 3,4,5-trisphosphate, a product of phosphatidylinositol 3-kinase. We have identified a homolog of **PTEN** in *Caenorhabditis elegans* and have found that it corresponds to the **daf-18** gene, which had been defined by a single, phenotypically weak allele, **daf-18** (e1375). By analyzing an allele, **daf-18**(nr2037), which bears a deletion of the catalytic portion of CePTEN/**DAF-18**, we have shown that mutation in **daf-18** can completely suppress the dauer-constitutive phenotype caused by

inactivation of *daf-2* or *age-1*, which encode an insulin receptor-like molecule and the catalytic subunit of phosphatidylinositol 3-kinase, respectively. In addition, *daf-18*(nr2037) dramatically shortens lifespan, both in a wild-type background and in a *daf-2* mutant background that normally prolongs lifespan. The lifespan in a *daf-18*(nr2037) mutant can be restored to essentially that of wild type when combined with a *daf-2* mutation. Our studies provide genetic evidence that, in *C. elegans*, the **PTEN** homolog **DAF-18** functions as a negative regulator of the DAF-2 and AGE-1 signaling pathway, consistent with the notion that **DAF-18** acts as a phosphatidylinositol 3,4,5-trisphosphate phosphatase in vivo. Furthermore, our studies have uncovered a longevity-promoting activity of the **PTEN** homolog in *C. elegans*.

L5 ANSWER 3 OF 5 MEDLINE
 AN 1999227332 MEDLINE
 TI Regulation of dauer larva development in *Caenorhabditis elegans* by *daf-18*, a homologue of the tumour suppressor **PTEN**.
 SO CURRENT BIOLOGY, (1999 Mar 25) 9 (6) 329-32.
 Journal code: B44; 9107782. ISSN: 0960-9822.
 AU Rouault J P; Kuwabara P E; Sinilnikova O M; Duret L; Thierry-Mieg D; Billaud M
 AB The tumour suppressor gene **PTEN** (also called MMAC1 or TEP1) is somatically mutated in a variety of cancer types [1] [2] [3] [4]. In addition, germline mutation of **PTEN** is responsible for two dominantly inherited, related cancer syndromes called Cowden disease and Bannayan-Ruvalcaba-Riley syndrome [4]. **PTEN** encodes a dual-specificity phosphatase that inhibits cell spreading and migration partly by inhibiting integrin-mediated signalling [5] [6] [7]. Furthermore, **PTEN** regulates the levels of phosphatidylinositol 3,4,5-trisphosphate (PIP3) by specifically dephosphorylating position 3 on the inositol ring [8]. We report here that the dauer formation gene *daf-18* is the *Caenorhabditis elegans* homologue of **PTEN**. **DAF-18** is a component of the insulin-like signalling pathway controlling entry into diapause and adult longevity that is regulated by the DAF-2 receptor tyrosine kinase and the AGE-1 PI 3-kinase [9]. Others have shown that mutation of *daf-18* suppresses the life extension and constitutive dauer formation associated with *daf-2* or *age-1* mutants. Similarly, we show that inactivation of *daf-18* by RNA-mediated interference mimics this suppression, and that a wild-type *daf-18* transgene rescues the dauer defect. These results indicate that **PTEN/daf-18** antagonizes the DAF-2-AGE-1 pathway, perhaps by catalyzing dephosphorylation of the PIP3 generated by AGE-1. These data further support the notion that mutations of **PTEN** contribute to the development of human neoplasia through an aberrant activation of the PI 3-kinase signalling cascade.

L5 ANSWER 4 OF 5 MEDLINE
 AN 1999178991 MEDLINE
 TI Regulation of the insulin-like developmental pathway of *Caenorhabditis elegans* by a homolog of the **PTEN** tumor suppressor gene.
 SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1999 Mar 16) 96 (6) 2925-30.
 Journal code: PV3; 7505876. ISSN: 0027-8424.
 AU Gil E B; Malone Link E; Liu L X; Johnson C D; Lees J A
 AB The human **PTEN** tumor suppressor gene is mutated in a wide variety of sporadic tumors. To determine the function of **PTEN** in vivo we have studied a **PTEN** homolog in *Caenorhabditis elegans*. We have generated a strong loss-of-function allele of the **PTEN** homolog and shown that the deficient strain is unable to enter dauer diapause. An insulin-like phosphatidylinositol 3-OH kinase (PI3'K) signaling pathway regulates dauer-stage entry. Mutations in either

the daf-2 insulin receptor-like (IRL) gene or the age-1 encoded PI3'K catalytic subunit homolog cause constitutive dauer formation and also affect the life span, brood size, and metabolism of nondauer animals. Strikingly, loss-of-function mutations in the age-1 PI3'K and daf-2 IRL genes are suppressed by loss-of-function mutations in the **PTEN** homolog. We establish that the **PTEN** homolog is encoded by **daf-18**, a previously uncloned gene that has been shown to interact genetically with the DAF-2 IRL AGE-1 PI3'K signaling pathway. This interaction provides clear genetic evidence that **PTEN** acts to antagonize PI3'K function in vivo. Given the conservation of the PI3'K signaling pathway between *C. elegans* and *mammals*, the analysis of **daf-18 PTEN** mutant nematodes should shed light on the role of human **PTEN** in the etiology of metabolic disease, aging, and cancer.

L5 ANSWER 5 OF 5 CAPLUS COPYRIGHT 2002 ACS

AN 2000:384548 CAPLUS

DN 133:39116

TI Genes and polypeptides involved in insulin signaling pathways for glucose tolerance, obesity, and longevity and their uses as therapeutic and diagnostic tools

SO PCT Int. Appl., 402 pp.
CODEN: PIXXD2

IN Ruvkun, Gary; Ogg, Scott

AB Disclosed herein are novel genes and methods for the screening of therapeutics useful for treating impaired glucose tolerance conditions, as well as diagnostics and therapeutic compns. for identifying or treating such conditions. The *Caenorhabditis elegans* metabolic regulatory genes daf-2 and age-1 encode homologs of the mammalian insulin receptor/phosphoinositol 3-kinase signaling pathway proteins, resp. Also, the *C. elegans* PKB kinase and AKT kinase act downstream of these genes, as their mammalian homologs act downstream of insulin signaling. The *C. elegans* **PTEN** lipid phosphatase homolog, **DAF-18**, acts upstream of AKT in this signaling pathway. Further, the DAF-16 forkhead protein represents the major transcriptional output of this insulin signaling pathway. Addnl. evidence indicates that the DAF-16, DAF-3, DAF-8, and DAF-14 transcriptional outputs of converging signaling pathways regulate metab. The congruence between the *C. elegans* and mammalian insulin signaling pathways strongly supports the contention that new genes identified in the *C. elegans* pathway also act in mammalian insulin signaling. Exemplary sequences and functional characteristics of the *C. elegans* daf genes and their human homologs are provided.

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2000033068	A1	20000608	WO 1999-US28529	19991202
W:	AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
US 2001029617	A1	20011011	US 1998-205658	19981203
EP 1163515	A1	20011219	EP 1999-960641	19991202
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO			

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L8 53 S L7 AND (MODULATE? OR INCREASE? OR DECREASE? OR ENHANCE? OR S
L9 53 SORT L8 PY
L10 3 S L9 NOT PTEN

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L10 ANSWER 1 OF 3 MEDLINE

AN 96170778 MEDLINE

TI The age-1 and daf-2 genes function in a common pathway to control the lifespan of *Caenorhabditis elegans*.

SO GENETICS, (1995 Dec) 141 (4) 1399-406.

Journal code: FNH; 0374636. ISSN: 0016-6731.

AU Dorman J B; Albinder B; Shroyer T; Kenyon C

AB Recessive mutations in two genes, *daf-2* and *age-1*, extend the lifespan of *Caenorhabditis elegans* significantly. The *daf-2* gene also regulates formation of an alternative developmental state called the dauer. Here we asked whether these two genes function in the same or different lifespan pathways. We found that the longevity of both *age-1* and *daf-2* mutants requires the activities of the same two genes, *daf-16* and **daf-18**. In addition, the *daf-2*(*el370*); *age-1*(*hx546*) double mutant did not live significantly longer than the *daf-2* single mutant. We also found that, like *daf-2* mutations, the *age-1*(*hx546*) mutation affects certain aspects of dauer formation. These findings suggest that *age-1* and *daf-2* mutations do act in the same lifespan pathway and extend lifespan by triggering similar if not identical processes.

L10 ANSWER 2 OF 3 MEDLINE

AN 95309673 MEDLINE

TI Genes that regulate both development and longevity in *Caenorhabditis elegans*.

SO GENETICS, (1995 Apr) 139 (4) 1567-83.

Journal code: FNH; 0374636. ISSN: 0016-6731.

AU Larsen P L; Albert P S; Riddle D L

AB The nematode *Caenorhabditis elegans* responds to conditions of overcrowding and limited food by arresting development as a dauer larva. Genetic analysis of mutations that alter dauer larva formation (*daf* mutations) is presented along with an updated genetic pathway for dauer vs. nondauer development. Mutations in the *daf-2* and *daf-23* genes double adult life span, whereas mutations in four other dauer-constitutive genes positioned in a separate branch of this pathway (*daf-1*, *daf-4*, *daf-7* and *daf-8*) do not. The **increased** life spans are **suppressed** completely by a *daf-16* mutation and partially in a *daf-2*; **daf-18** double mutant. A genetic pathway for determination of adult life span is presented based on the same strains and growth conditions used to characterize *Daf* phenotypes. Both dauer larva formation and adult life span are affected in *daf-2*; *daf-12* double mutants in an allele-specific manner. Mutations in *daf-12* do not extend adult life span, but certain combinations of *daf-2* and *daf-12* mutant alleles nearly quadruple it. This synergistic effect, which does not equivalently extend the fertile period, is the largest genetic extension of life span yet observed in a metazoan.

L10 ANSWER 3 OF 3 MEDLINE

AN 92120509 MEDLINE
TI Genetic analysis of chemosensory control of dauer formation in
Caenorhabditis elegans.
SO GENETICS, (1992 Jan) 130 (1) 105-23.
Journal code: FNH; 0374636. ISSN: 0016-6731.
AU Vowels J J; Thomas J H
AB Dauer larva formation in Caenorhabditis elegans is controlled by chemosensory cells that respond to environmental cues. Genetic interactions among mutations in 23 genes that affect dauer larva formation were investigated. Mutations in seven genes that cause constitutive dauer formation, and mutations in 16 genes that either block dauer formation or result in the formation of abnormal dauers, were analyzed. Double mutants between dauer-constitutive and dauer-defective mutations were constructed and characterized for their capacity to form dauer larvae. Many of the genes could be interpreted to lie in a simple linear epistasis pathway. Three genes, daf-16, **daf-18** and daf-20, may affect downstream steps in a branched part of the pathway. Three other genes, daf-2, daf-3 and daf-5, displayed partial or complex epistasis interactions that were difficult to interpret as part of a simple linear pathway. Dauer-defective mutations in nine genes cause structurally defective chemosensory cilia, thereby blocking chemosensation. Mutations in all nine of these genes appear to fall at a single step in the epistasis pathway. Dauer-constitutive mutations in one gene, daf-11, were strongly **suppressed** for dauer formation by mutations in the nine cilium-structure genes. Mutations in the other six dauer-constitutive genes caused dauer formation despite the absence of functional chemosensory endings. These results suggest that daf-11 is directly involved in chemosensory transduction essential for dauer formation, while the other Daf-c genes play roles downstream of the chemosensory step.

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L9 53 SORT L8 PY
L10 3 S L9 NOT PTEN
L11 43 S DAF-18 OR DAF18
L12 12 DUP REM L11 (31 DUPLICATES REMOVED)
L13 12 SORT L12 1-12 PY

L Number	Hits	Search Text	DB	Time stamp
1	2	("6225120").PN.	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/02/26 14:26
7	72	DAF-\$5	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/02/26 14:26
13	4	DAF-\$5 and DAF-18	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/02/26 14:31
19	39	glucose AND diabet\$5 AND obes\$10 AND elegans	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/02/26 14:32
25	5	(glucose AND diabet\$5 AND obes\$10 AND elegans) and DAF-\$5	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/02/26 14:35
31	4	DAF-\$5 and PTEN	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/02/26 14:35